Brandeis University

Benjamin and Mae Volen National
Center for Complex Systems

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The M.R. Bauer Foundation Colloquium Series, Distinguished Lecturer Series, Annual Scientific Retreat, and Summer Science Research Fellowship

The M.R. Bauer Foundation Colloquium Series, Distinguished Lecturer Series, Annual Scientific Retreat, and Summer Science Research Fellowship 2016-17 Summary

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The 2016-2017 M.R. Bauer Foundation

Colloquium Series, Distinguished Lecturer Series, Annual Scientific Retreat, and Summer Science Research Fellowship

Introduction

In these challenging times, science serves as bedrock and lodestar. The importance of pushing the boundaries of knowledge forward is ever increasing.

Science is the foundation upon which we build knowledge and policy — a complex world requires that we ask good questions and resolve challenges with tested solutions. While the public domain can be raucous, reason remains a guardrail against excess.

Science is needed now more than ever, and can be more influential than ever before. Science is illuminating every aspect of the world, from nanoparticles and neurons, to space. Scientific discovery still has the capacity to transcend the commonplace and the mundane. We are wise to remember that research can be a source of inspiration for everyone.

Scientists are fulfilling these dual roles — ambitious investigators on the one hand and champions of reason on the other — with aplomb and skill. We are communicating the compelling features of our work and speaking to the emotional appeal of science. Our response to these new responsibilities fills me with optimism.

Proudly, Brandeis is cultivating aspiring researchers who adhere to the most rigorous standards and are capable of promoting science. They are demonstrating daring, courage, and resilience. They, too, give me hope for the future of neuroscience and the place of science in society.

The M.R. Bauer Foundation recognizes the importance of training emerging scientists and replenishing faculty, and we are honored that the Foundation invests in the Volen Center and the Division of Science. The impressive assortment of Foundation-sponsored programs, detailed in this brochure, benefit the Brandeis community and those with whom we work. It is a cherished partnership that has ongoing and lasting impact.

Each of us is an ambassador of science. Together, we are bringing science to the world, changing our respective fields, and preparing those who will inherit, and advance, our discoveries.

Leslie C. Griffith, MD, PhD
Nancy Lurie Marks Professor of Neuroscience and
Director, Volen National Center for Complex Systems

The M.R. Bauer Foundation Colloquium Series Summaries

Introduction

The human brain comprises tens of billions of neurons that form intricate neural networks. Our ability to walk, move, learn and think, are dependent upon proper functioning of these networks (disease and dementia can result from their disruption). Proper understanding of how the networks are regulated, and how they can be disrupted in disease, are necessary in order to pave the way for new treatments that can slow, arrest, or reverse the effects of disease.

The 2016-17 M.R. Bauer Foundation Colloquium Series explored new developments in the understanding of the brain: how we learn, how we pass our knowledge onto our progeny, how we are rewarded for behaviors, and how neural compromise leads to disease. Seven distinguished scientists offered unique insights into the processes of learning and memory, reward, and the effects of stress and aging on neurons. Each speaker has presented a summary of his or her work, which is preceded by a brief introduction (in italics) explaining the presentation in a more general framework of synaptic transmission in the face of a plastic, changing brain.

Giovanni Bosco, PhD
Oscar M. Cohn Professor
Department of Molecular and Systems Biology
Dartmouth Geisel School of Medicine
(September 13, 2016)

Social Learning and Trans-Generational Inheritance of Behavior in *Drosophila*: Revisiting Darwin's "Gemmule" Hypothesis

Survival of the fittest depends not just on strength, but also on cunning. How do smaller animals learn to recognize and avoid predators over generations? Dr. Bosco's work focuses on the learning and inheritance of avoidance behaviors in the fruit fly. He and his lab have shown that fruit flies exposed to a predator (a parasitic wasp) are able to not only teach other flies about the threat, but also to pass this information epigenetically to future generations. Female fruit flies exposed to a wasp show genetic changes that help future generations avoid the predator. These genetic changes are also evident in the eggs of this female. Future work in Dr. Bosco's lab will focus on exactly how this process works.

We have started a new project in which we have developed a novel paradigm for studying long-term memory in *Drosophila*. This project has three components to it: First, although most other *Drosophila* learning and memory assays use classical conditioning to elicit an associative memory, our new method uses an innate non-associative response to an ecologically-relevant stimulus (a predatory wasp). Second, flies exposed to predators engage in social interactions, whereby naive flies learn and remember as if they had seen the predator. To our knowledge, this is the first example of fly-to-fly communication about a specific environmental threat that is strictly communicated via visual cues. We wish to further develop this approach to understand the genetic basis of memory formation and maintenance. Third, we have discovered that brain activity elicited by this predator can change germline physiology and reprogramming of epigenetic germline information. Exposure of females to predators induces epigenetic reprogramming of eggs and leads to the inheritance of specific behaviors that help subsequent generations to avoid predation by this same predatory wasp. Inheritance of this behavior persists for five generations and acts through a novel (and yet to be described) mechanism. Current work in the Bosco Lab seeks to understand how brain activity changes germline information, and how this information can be passed down from one generation to the next.

Gerald Rubin, PhD
Vice President, Howard Hughes Medical Institute, and
Executive Director,Janelia Research Campus
(November 8, 2016)

Learning and Memory in *Drosophila*

Learning and memory can be studied at many different levels, from human behaviors, down to neurons in a dish. To understand how memories are formed at the level of cells and circuits, a model organism, like the fruit fly, can be used. In order to understand how circuits change with learning, a detailed map of the fly brain is required. Dr. Rubin discussed his work on learning and memory using the fly olfactory system. His work has shown that individual parts of a memory, or engrams, are stored in multiple sub-circuits, which can be combined to guide behavior. These sub-circuits have different mechanisms for creating and changing memory. Future work, Dr. Rubin says, will examine whether this data will help in the understanding of how the brain uses memory to guide behavior.

To probe the workings of the nervous system, we will need detailed anatomical information and the ability to assay and manipulate the function of individual neuronal cells and cell types. The intellectual framework for such an approach has been articulated by several research groups over the past 10 years. But tools have been inadequate for the job. In my lecture, I discussed efforts to develop and apply some of the tools that will be required for a comprehensive analysis of the anatomy and function of the small brain of *Drosophila melanogaster* at the level of individual cell types and circuits using examples from our recent work on the mechanisms of learning and memory.

Experiments aimed at uncovering the mechanisms by which different forms of memory are established and maintained, and then coherently coordinated to drive behavior, are facilitated by using a model system in which the relevant cells and circuits can be identified and manipulated either individually, or in specific combinations. In my lecture, I described experiments performed in such a model system, the *Drosophila* olfactory circuit.

Animals use memories of past events to predict the future. In some cases, an animal is best served by making a prediction based solely on their most recent experience. In others, a series of experiences is integrated to make a probabilistic prediction, discounting an event experienced only once. How are such different strategies implemented in the brain? Our results suggest that individual components of a memory — often called engrams — are simultaneously stored in distinct sub-circuits whose outputs can then be combined upon recall to affect behavior. These sub-circuits vary in their rules for writing, updating and retaining these engrams, having differences in synaptic plasticity and circuit properties.

Will these data, combined with theory and modeling, be sufficient to understand how a brain executes complex computations to achieve sophisticated behaviors? Time will tell.

Rick Morimoto, PhD
Professor
Department of Molecular Biosciences
Northwestern University
(November 29, 2016)

Proteostasis: Stress Responses and Chaperone Networks in Aging and Disease

As the population ages, the incidence of age-related dementia and conditions such Alzheimer's disease is increasing. While it is understood that the build-up of damaged proteins in the brain is associated with different forms of dementia, how the damage to these proteins occurs is less clear. Dr. Morimoto and his lab are examining how aging and cell response to different stressors affect proteins. Understanding this process could help in the discovery of new treatments or ways to prevent age-related dementia.

Increased lifespan is accompanied by elevated risks for dementia, neurodegeneration and other age-associated degenerative diseases. A common feature of aging and disease is the accumulation of damaged proteins that accumulate in aggregates and amyloid species that interfere with cellular function. The appearance of this "molecular clutter" is a consequence of inherent protein metastability and failure of the protein quality control machinery during aging and stress. In my talk, I examined how the proteostasis network (PN) of molecular chaperones, transport processes, ubiquitin-dependent proteasomes and autophagic machines is essential for proteome health and to prevent the accumulation of protein aggregates. During aging, the composition of the PN and response to heat shock and other cellular stress conditions are compromised with an abrupt transition occurring at reproductive maturity. This signal from the germline stem cells involves an epigenetic mark leading to an irreversible repression of the heat shock response. Likewise, at the organismal level, cell non-autonomous signaling between neurons and surrounding tissues regulates the response to heat shock, and from tissues expressing mutant proteins that communicate to receiving tissues to activate the protective induction of chaperones. Organismal proteostasis therefore represents balance and coordination among multiple cell stress responses to ensure cellular and tissue health and longevity.

Daniel Wesson PhD
Assistant Professor
Department of Pharmacology and Therapeutics
Case Western Reserve University
(December 6, 2016)

Identifying New Brain Mechanisms for Sensory Processing and Motivating Behaviors

How many times has the promise of a slice of piping hot pizza helped with the motivation to go to the gym? Especially since the pizza place is right next to the gym, and the delicious smell wafts over to the gym door? Dr. Wesson discussed his work on how olfactory cues can be used to motivate behaviors in the rodent. This work has shown that a particular place in the olfactory processing area of the brain, the olfactory tubercle, may encode smells differently if they predict a reward or if they are a reward. His future work will examine how the activity in this area correlates with attention and other behaviors.

A major question of wide importance is how animals engage their sensory environment to inform decisions and guide behaviors. This broad question holds implications for understanding not only the normal functioning of the nervous system, but also for elucidating manners whereby neurological disorders impact the brain. The research in our lab addresses this question by studying the neural centers in the mammalian olfactory system responsible for processing odors and for generating odor perception.

The research discussed in this talk builds upon recent discoveries by our lab that provide insights into the function of a previously underappreciated brain region, the ventral striatum's olfactory tubercle. Our work, which largely utilizes physiological methods in behaving rodents, has defined the essential principles of odor information processing in the olfactory tubercle. Additionally, we have uncovered evidence that the olfactory tubercle flexibly encodes odors conditioned to predict rewards, goal-directed instrumental behaviors, and even rewards themselves. These results suggest a role for the olfactory tubercle in not just processing odor information, but additionally in integrating odors with a motivationally dependent and cognitively shaped behavioral response.

In this talk, I provided an overview of these initial insights and highlight ongoing projects that attempt to causally link the activity of olfactory tubercle neurons to motivated behaviors. I also defined the influence of cognitive states, specifically selective attention, on odor-guided behaviors and odor coding in the olfactory tubercle. Together, the results of these investigations will provide fundamental information on the mechanisms of olfaction and motivated behaviors.

Franck Polleux, PhD
Professor
Department of Neuroscience
Columbia University
(January 24, 2017)

Novel Mechanisms Regulating Calcium Homeostasis in Neurons Through Control of Mitochondria Function and Mitochondria-ER Interface

Neurons are a unique type of cell in the body. They have distinct features, the axon and dendrites that allow communication with other neurons. Dr. Polleux and his lab are researching factors involved in the development of these distinct features. He discussed the protein LKB1, which he has shown is necessary for the regulation of an important part of neuronal growth – capturing mitochondria. Mitochondria are structures that generate power for cells. He also discussed the importance of mitochondrial size in the axon and dendrites. Mitochondria are longer in the dendrites than in the axon, and this feature has proven to be important for how the cells communicate with other neurons.

Our laboratory is focusing on the cellular and molecular mechanisms underlying the development of the mammalian brain. Neurons are among the most highly polarized cells in our body. Neurons are truly unique cells with regard to their size and morphological complexity. They are highly compartmentalized elaborating a single long axon (transmitting information to other neurons) and multiple dendrites (that receive thousands of synaptic inputs made by the axons of other neurons). We have identified several new signaling pathways regulating the development of neuronal morphology including axonal and dendritic growth, guidance and branching. My seminar focused on recent advances from our lab in understanding the function of a specific signaling pathway centered around kinase LKB1. LKB1 regulates terminal axon branching through regulation of a novel cell biological step: the capture of mitochondria at presynaptic boutons (Courchet, Lewis et al. Cell 2013). We found that during development, synapses made along the axon (called presynaptic boutons) capture a single mitochondria which seems largely dispensable for ATP production, but plays a critical role in regulating cytoplasmic calcium dynamics during neurotransmitter release (Kwon et al. PLoS Biology 2016).

I also presented preliminary evidence demonstrating the drastic difference in morphology between axonal and dendritic mitochondria in cortical pyramidal neurons. In the dendrites of these large neurons, mitochondria are long (~5-15 microns in length) and form an extended network covering >80% of the dendritic tree. In contrast, axonal mitochondria are small (~1 micron in length) and are mostly localized at presynaptic boutons covering only 5-10% of the total axonal length. This suggested that mitochondrial fission must be dominant in axons, whereas fusion must be dominant in the dendrites of the same neurons. This degree of fission/fusion compartmentalization was never explored before and we identified the mitochondrial fission factor (a Drp1 'receptor' called Mff) that regulates mitochondria size in the axon specifically. Upon knocking down Mff, axonal mitochondria become very long, as observed in dendrites, but they are still trafficked normally and captured presynaptically. We demonstrate that compared to control, these long mitochondria offered a larger volume for calcium uptake and therefore lowered the concentration of cytoplasmic calcium presynaptically during evoked release, significantly lowering presynaptic release probability. Our results demonstrate that in axons, mitochondria size is regulated by a high level of Mff-dependent fission, which plays a critical role in determining their calcium uptake capacity, thereby regulating presynaptic release properties.

Leo Belluscio, PhD
Senior Investigator
Developmental Neural Plasticity Section
National Institute of Neurological Disorders and Stroke
National Institutes of Health
(March 7, 2017)

Using the Olfactory System to Study Neurodegeneration

Many patients with Alzheimer's disease may find that they have lost their sense of smell. This can occur very early in the course of the disease, perhaps even before problems with memory become noticeable. Dr. Belluscio has used a mouse model of Alzheimer's disease to pinpoint the molecular basis of the loss of smell. His group has shown that by blocking a particular protein, olfactory neurons are able to recover, even after extensive damage. His future research will try to determine if the same process is present in human Alzheimer's disease patients.

The regenerative ability of the mammalian olfactory system, combined with is its precisely defined anatomical maps, provides an ideal platform to study neural circuit disruption and repair.

We took advantage of this to develop an olfactory-based mouse model of Alzheimer's disease (AD) that can be regulated in vivo through drug application. Our goal was to gain insight into the early loss of olfactory function that is commonly reported in AD patients. Using this transgenic mouse model, we reversibly expressed a humanized mutant form of the Amyloid Precursor Protein (hAPP) in olfactory sensory neurons (OSNs) and revealed clear neural apoptosis in hAPP expressing neurons at a very early age. We further determined that by turning off hAPP expression after extensive degeneration had occurred the olfactory system is still capable of recovering both in its neural structure and function. Finally, we show that the observed OSN loss is through a cell-autonomous mechanism that may mark an early cellular phase of disease. Future studies will determine if similar transduction pathways mediate the olfactory loss in AD patients.

Ravi Allada, PhD
Edward C. Stuntz Distinguished Professor
Chair, Department of Neurobiology
Northwestern University
(April 25, 2017)

Circadian Clocks: From Fruit Flies to Fly Balls

Conditions such as Alzheimer's or Huntington's disease are associated with the accumulation of proteins that destroy certain nerve cells. The death of these neurons leads to the symptoms experienced by patients, such as movement problems in Huntington's disease. More and more evidence is suggesting that circadian clocks may be disrupted early in the disease. Circadian clocks set the daily rhythm of processes in the body. Dr. Allada and his lab have used the fruit fly as a model for Huntington's disease. Their research has determined that a protein associated with Huntington's disease (mHtt) impairs circadian rhythms before symptoms appear. Altering the circadian clocks changed the rate of neuron death, due to mHtt. Dr. Allada's future work will attempt to find the cellular pathways that link mHtt and circadian clocks.

Neurodegenerative diseases, such as Alzheimer's and Huntington's, commonly involve the accumulation and aggregation of neurotoxic proteins that impair and ultimately destroy specific neurons. Identifying processes that can slow neurodegeneration, especially before irreversible cell death, is a major challenge for the development of effective therapeutics. Accumulating evidence suggests that disrupted clocks are associated with, and even potentially alter, neurodegeneration at this early stage. To address the mechanistic relationship between circadian clocks and neurodegenerative diseases, we are using Huntington's disease (HD) as a model. HD is caused by a triplet repeat expansion resulting in an expansion of a polyglutamine repeat in the Huntington protein (mHtt). Accumulation of mHtt results in degeneration of striatal, as well as cortical neurons, resulting in the characteristic motor and cognitive symptoms, and ultimately death. Considerable evidence from human and animal studies indicates that mHtt impairs circadian rhythms often before characteristic motor symptoms are even evident. In fact, master circadian pacemaker neurons are lost in HD patients. Yet little is known about the molecular mechanisms by which mHtt impairs circadian rhythmicity. In addition, it is unknown if circadian clocks, in turn, can modulate HD pathogenesis. To study the interplay between clocks and HD, the fruit fly *Drosophila*, a well-established model organism in the study of neurodegenerative disease and circadian clocks, has been employed. Both environmental and genetic perturbations of the circadian clock were shown to alter mHtt-mediated neurodegeneration, revealing that circadian clocks are not only a target of mHtt but may also be an important player in mediating mHtt-mediated pathogenesis. To identify potential genetic pathways that mediate the effect of the clock on mHtt, a novel behavioral platform has been developed for screening HD modifiers that would allow the identification of those genes that can modify pre-degenerative/functional and/or cell death effects of mHtt. As part of this screen, several novel pathways that mediate mHtt effects on behavior have been discovered, most notably the RNA binding protein Ataxin2. In addition, the molecular mechanisms by which novel modifiers function were explored in terms of mHtt inclusions, molecular clocks, and cell death, revealing effects on pre-degenerative neuronal dysfunction, as well as cell death. These studies exploit the advantages of the *Drosophila* system including the deep conservation with vertebrate models of circadian clocks and mechanisms of mHtt pathogenicity. High throughput fly genetics will be applied to reveal the elusive molecular and cellular pathways that bi-directionally link mHtt to clock disruption, a relatively understudied area of HD pathology and thus one ripe for the discovery of novel mechanisms.

The M.R. Bauer Foundation Distinguished Guest Lecturer Series

Introduction

Every year, the M.R. Bauer Distinguished Lecturer program brings to campus two renowned visitors who spend a full week at Brandeis. These weeklong visitors present talks to small and large groups, visit center laboratories, and engage students, postdoctoral fellows, and faculty in informational and highly interactive conversations about shared areas of research interests. This year, our esteemed lecturers were Huda Y. Zoghbi, a professor at the Baylor College of Medicine and an investigator with the Howard Hughes Medical Institute; and Casper Hoogenraad, a professor of cell biology from Utrecht University.

Huda Y. Zoghbi, MD
Ralph D. Feigin Professor, Baylor College of Medicine
Investigator, Howard Hughes Medical Institute
Director, Jan and Dan Duncan Neurological Research Institute at
Texas Children's Hospital
(November 1, 2016)

Rett Syndrome: From the Clinic to Genomes, Epigenomes, and Neural Circuits

Rett syndrome is a developmental disorder that becomes apparent in girls, early in life. Like autism, children with Rett syndrome appear to develop normally only to regress as they get older. Language and social interaction skills are lost first, followed by movement and other neurological problems. Dr. Zoghbi discussed her work focused on the genetics behind the syndrome. An early discovery was the identification of the MECP2 gene mutation responsible for Rett syndrome (as well as many other neuropsychiatric disorders). Dr. Zoghbi has developed a mouse model of Rett syndrome, which has allowed her to study the brain circuits and signaling chemicals (neurotransmitters) affected by the mutation. This model has helped her to pinpoint areas of possible treatment. Deep brain stimulation (inducing activity in a brain area) of the hippocampus improves learning and memory in Rett mice. Treatments to reduce levels of the MECP2 protein, which are very high in Rett syndrome, reduced many symptoms in mice. These exciting advances may offer future areas for treatment in children who develop this syndrome.

When I was a resident in pediatric neurology at Texas Children's Hospital in Houston, I met a patient who changed the course of my life. Her name was Ashley, and she had been perfectly healthy until she was about two years old. Then she lost interest in socializing, stopped greeting her father when he came home from work, and seemed to forget the words she had just been happily babbling only weeks before. Instead, she just sat and wrung her hands incessantly. She had a hard time walking, alternated between holding her breath and hyperventilating, and developed features of autism. Her symptoms and disease course matched those in a paper describing a new condition called Rett Syndrome, and it was clear to me that I was seeing this syndrome in real life. A week later, I saw another girl who was diagnosed with cerebral palsy, and I became seriously interested in research, because it was just heartbreaking not to be able to offer the families any sort of treatment or hope.

I soon found a number of patients with Rett Syndrome, and two things convinced me that it had to be genetic in origin, despite the fact that the cases I was seeing were all sporadic. First, the disease appeared to affect only females, which suggested the gene could be on the X chromosome. Second, the timeline of progression — loss of language and social interaction first, then development of motor problems, then epilepsy and autonomic dysfunction — was remarkably consistent, despite the variability in the severity of symptoms. But some clinicians doubted that Rett Syndrome was actually a distinct clinical entity at all. Many scientists considered it a fool's errand to pursue the genetic basis of a (mostly) sporadic disorder, so the early years were pretty discouraging. When I located a couple of families with more than one affected individual, this helped us narrow our search to a specific region on the X chromosome. Finally, 16 years after seeing my first Rett patient, my lab identified the responsible gene as *methyl cytosine-binding protein 2* (*MECP2*). This gene was discovered in the early '90s by Adrian Bird, who found that it is involved in control of gene expression. Our discovery opened up the field of studying epigenetics in neurodevelopment.

Identifying the gene enabled us to make mouse models of different *MECP2* mutations and helped us really begin to understand Rett syndrome and related diseases. The variety of phenotypes that can be caused by mutations in *MECP2* is very broad, ranging from neonatal encephalopathy and death within one year in male infants, to classic Rett syndrome, to simple autism or very mild learning disability, if the female child has a very mild mutation that preserves most of the protein's function or very favorable X inactivation (i.e., the chromosome with the mutated *MECP2* gene is preferentially silenced, so that it is mostly the "good" MeCP2 protein that gets expressed). Some children even develop an early-onset schizophrenia or bipolar disorder. To see what happens when the brain gets too much MeCP2, we created mice that overexpress the protein at twice or three times its normal levels. These mice developed a distinct neurological phenotype that enabled us to go back to the clinic to look for children who had the same symptoms. It turns out that chromosomal duplications of the region of the chromosome containing *MECP2* also cause a neurodevelopmental disability, a syndrome of cognitive, affective, and motor impairments in boys. We now know that MeCP2 Duplication Syndrome is one of the most common X-linked intellectual disability syndromes in male children.

We have also learned that a few thousand genes are affected by changes in MeCP2 function. Many of the ~2500 genes that we've identified are also associated with autism and other neuropsychiatric disorders. With so many genes affected simultaneously, any gene-based treatment, or efforts to target one specific pathway pharmacologically would be very unlikely to succeed. So we decided to study the neurotransmitters and brain circuits that are most affected in MeCP2 disorders. We discovered that partial reductions of GABAergic or glutamatergic signaling reproduces much of the Rett syndrome phenotype, which led us to propose that many genes involved in GABAergic or glutamatergic signaling (including synthesizing enzymes or transporters) are candidate genes for neuropsychiatric disorders. In studying the electrophysiological behavior of these neurons, which are inhibitory and excitatory, respectively, we also realized that modulating neural circuits in Rett syndrome with deep-brain stimulation (DBS) might be able to provide an avenue for treatment. To test this hypothesis, we focused on learning and memory, which are functions of a healthy hippocampus. We took female Rett syndrome mice and, in collaboration with Dr. Jianrong Tang, performed DBS in the hippocampus for one hour a day over a period of two weeks. Remarkably, after this treatment the Rett mice performed as well as wild-type mice in specific tests of learning and memory, such as the Morris water maze. The treated mice also showed improvements in long-term potentiation (LTP), a sign of enhanced plasticity at the physiological level, and also showed a restoration of hippocampal neurogenesis to the level observed in wild-type animals. DBS is an invasive but well-established procedure that has the potential to improve life for Rett children, but much more testing needs to be done.

Our most exciting prospect for treatment is in the context of MeCP2 duplication syndrome. Here the problem is that there is twice as much MeCP2 protein in the brain as there should be, and we need to reduce the levels back to normal. We know that if you genetically delete one of the two MeCP2-coding alleles in the duplication mice after they are symptomatic, all the features of the disease disappear — the mice become normal. We have therefore collaborated with Ionis Pharmaceuticals to develop antisense oligonucleotides to suppress production of MeCP2 protein. Antisense oligonucleotides, or ASOs, are small, modified DNA molecules that bind the mRNA. When this happens, an enzyme called RNAseH will detect the RNA-DNA pairing and will degrade the RNA so that no protein will be made from this allele. Because children with MeCP2 Duplication Syndrome already have had symptoms for years by the time of diagnosis, we allowed the duplication mice to mature into adults and develop all the features of the syndrome, before administering ASOs that target the extra copy of MeCP2. We infused the ASO directly into the ventricles of the brain over a period of four weeks and succeeded in normalizing the levels of MeCP2. The ASO treatment also eradicated the symptoms of MeCP2 duplication mice, from their extreme anxiety and avoidance of social interaction, to their seizures. Even older adult mice of six or seven months of age that have had the disease features for many months can be restored to health with the ASO treatment.

In conclusion, we've learned that the brain is highly sensitive to the levels of MeCP2 protein. I call it the "Goldilocks" principle. You have to have it just right, and I am sure there are some patients that might have 60 percent, or 40 percent of the protein, and they might present with partial symptoms. I hope that one day we will be able to give back to the patients and their families by developing better therapeutics.

With that, I would like to thank those who have contributed to the work, particularly Ruthi Amir, who stuck with me and kept sequencing genes until she found the right one; and all the students, fellows and collaborators who have contributed to various aspects of our Rett studies over the years.

I am very grateful to the Rett syndrome and *MECP2* disorders families, and to all the funding agencies (particularly to the Howard Hughes Medical Institute whose support really enabled me to continue to study Rett), as well as the NIH, the Rett syndrome Research Trust, International Rett Syndrome foundation, the Keck Foundation, and the Simons Foundation.

Casper Hoogenraad, PhD
Professor
Department of Molecular and Cell Biology
Utrecht University
(March 28, 2017)

Cytoskeleton-Based Mechanisms Underlying the Biology and Diseases of the Nervous System

During brain development, neurons must migrate and form connections. The correct formation of neural circuits depends on multiple factors working together. The movement of axons and dendrites (the parts of the neuron that send and receive messages from other neurons) depend on microtubules. Dr. Hoogenraad discussed his work examining the protein TRIM46. He and his lab have determined that this protein is essential for proper microtubule formation, which, in turn, is essential for normal neural circuit formation. Dr. Hoogenraad also discussed the association of another mutation affecting the protein KBP and alterations in the microtubule and transport of messages. These abnormalities in development may be the basis of certain neurological disorders.

The formation of complex nervous systems requires cytoskeleton-based processes that coordinate proliferation and differentiation of neurons. Neuronal cells undergo major developmental changes as they migrate, develop axons and dendrites, and establish synaptic connections. The structural organization and dynamic remodeling of the neuronal cytoskeleton contribute to all these morphological and functional changes in neurons. Along with the actin cytoskeleton, the assembly, organization, and remodeling of the microtubule cytoskeleton are essential to successfully complete all the different stages of neuronal development. Microtubule-based motor proteins, such as kinesin and dynein, recognize the intrinsic asymmetry of the microtubule lattice and drive cargo transport to either the microtubule plus-end, or minus-end. In various model systems, it has been shown that the microtubule arrays (within axon and dendrites) are highly organized, with respect to their intrinsic polarity, and that this specific microtubule organization is essential to direct polarized cargo transport. In addition, alterations in microtubule organization and cargo trafficking have been described in many neurodegenerative diseases. Thus, while the importance of the microtubule cytoskeleton for proper intracellular trafficking and cargo sorting is unambiguous, how the microtubule in axon and dendrites are organized, and how cargo trafficking is controlled, is largely unknown.

In the first part of the talk, I discussed our efforts to identify the molecular processes that control microtubule organization and dynamics during the different stages of neuronal development. Our recent work indicates that the formation of parallel microtubule bundles in the proximal axon initiates neuronal polarity. We found that the tripartite motif (TRIM) containing protein, TRIM46, plays an instructive role in the initial polarization of neuronal cells. TRIM46 is specifically localized to the newly specified axon and, at later stages, partly overlaps with the axon initial segment (AIS). TRIM46 specifically forms closely spaced parallel microtubule bundles, oriented with their plus-end out. Without TRIM46, all neurites have a dendrite-like mixed microtubule organization resulting in Tau missorting and altered cargo trafficking. By forming uniform microtubule bundles in the axon, TRIM46 is required for neuronal polarity and axon specification in vitro and in vivo. Our data support a model in which TRIM46 defines a unique axonal cytoskeletal compartment for regulating microtubule organization during the early stages of neuronal development.

In the second part of the talk, I discussed a new regulatory mechanism for microtubule-based cargo transport. Previous studies showed homozygous nonsense mutations in kinesin-binding protein (KBP)/KIAA1279 cause the neurological disorder Goldberg-Shprintzen syndrome (GOSHS), which is characterized by intellectual disability, microcephaly and axonal neuropathy. We found that KBP regulates kinesin activity by interacting with the motor domains of a specific subset of kinesins to prevent their association with the microtubule cytoskeleton. The KBP-interacting kinesins include cargo-transporting motors such as kinesin-3/KIF1A. We found that KBP inhibits KIF1A-mediated synaptic vesicle transport in cultured hippocampal neurons and *C. elegans* PVD sensory neurons. In contrast, depletion of KBP results in the accumulation of KIF1A motors and synaptic vesicles in the axonal growth cone. Our data indicates that KBP functions as a specific kinesin inhibitor that modulates synaptic cargo motility. We propose that misregulation of KBP-controlled kinesin motors may represent the underlying molecular mechanism that contributes to the neuropathological defects observed in GOSHS patients.

The Volen National Center for Complex Systems Scientific Retreat 2016

Introduction

The Volen National Center for Complex Systems held its annual scientific retreat on October 17, 2016. The event took place at the Charles River Museum of Industry and Innovation in Waltham, Mass. This year's theme was "Dynamics of Complex Systems." Emery Brown, from the Massachusetts Institute of Technology was our keynote speaker and he wrapped up the day with his seminar about the effects of anesthesia on the unconscious brain. In addition to Dr. Brown, we invited four new Brandeis assistant professors to discuss their work in complex systems. (Unfortunately, Amy Lee had to cancel due to illness.)

Holding the retreat off campus encourages the faculty, students and postdoctoral fellows who attend to interact in new ways. Being removed from familiar surroundings fosters connections and communication that lead to interdisciplinary and innovative collaborations that are much less likely to occur in the daily confines of the lab.

As the summaries on the following pages make clear, the 2016 retreat offered a view at the amazing research being pursued at Brandeis. Each project brings a better understanding of the complex systems around us.

The Volen National Center for Complex Systems Scientific Retreat

Schedule

October 17, 2016

8:30 a.m.
Arrival and Check-in

9:00 a.m.
Maria-Eirini Pandelia, Brandeis
“Digging Up Nature’s Mechanisms: Surprises by Enzymes With Novel Metallocofactors”

10:00 a.m.
Ben Rogers, Brandeis
“Using DNA to Program Pathways in Complex Self-Assembly”

11:00 a.m.
Poster Session

12:30 p.m.
Lunch

1:30 p.m.
Keynote Speaker
Emery Brown, MIT
“The Dynamics of the Unconscious Brain Under General Anesthesia”

2:30 p.m.
Break

2:45 p.m.
Tijana Ivanoic, Brandeis
“Influenza Membrane Fusion: Insights From Single Virions Into Potential Avenues for Viral Evolvability”

3:45 p.m. (Cancelled)
Amy S. Y. Lee, Brandeis
“EIF3-Directed Translation Regulation During Cell Growth and Differentiation”

4:45 p.m.
Departure

Emery Brown
Department of Medical Engineering
and Neuroscience
Massachusetts Institute of Technology
(October 17, 2016)

The Dynamics of the Unconscious Brain Under General Anesthesia

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The experience of being under anesthesia is a strange one. How do these medications block consciousness, pain and movement, leaving us unable to recall what has been happening around us? Dr. Emory Brown discussed his work measuring brain activity in patients under general anesthesia. He has found that the altered states of consciousness are associated with oscillations, or regular bursts of brain activity. These oscillations make it more difficult for brain areas to communicate with one another. Dr. Brown also discussed results showing that the response to anesthesia changes with the type of medication used and among different age groups.

General anesthesia is a man-made, drug-induced process that has enabled the safe and human provision of invasive diagnostic and surgical care for 170 years. During the last 10 years, our laboratory has helped define the neurophysiological mechanisms through which anesthetics induce altered arousal states. We discuss the implications of these new insights for creating translational opportunities in anesthesiology, in other fields of clinical neuroscience, and for gaining a new, fundamental understanding of how the brain’s arousal systems work.

General anesthesia is comprised of five behavioral states: unconsciousness, amnesia (loss of memory), analgesia (loss of pain sensation), akinesia (immobility), and hemodynamic stability with control of the stress response. Our work shows that a primary mechanism through which anesthetics create these altered states of arousal is by initiating and maintaining highly structured oscillations. These oscillations impair communication among brain regions. We illustrate this effect by presenting findings from our human studies of general anesthesia using high-density EEG recordings and intracranial recordings. These studies have allowed us to give a detailed characterization of the neurophysiology of loss and recovery of consciousness due to propofol. We show how these dynamics change systematically with different anesthetic classes and with age. We present a neuro-metabolic model of burst suppression, the profound state of brain inactivation seen in deep states of general anesthesia. We use our characterization of burst suppression, to implement a closed-loop anesthesia delivery system for control of a medically induced coma. Finally, we demonstrate that the state of general anesthesia can be rapidly reversed, by activating specific brain circuits. The success of our research has depended critically on tight coupling of experiments, signal processing research and mathematical modeling.

Maria-Eirini Pandelia, PhD
Department of Biochemistry
Brandeis University
(October 17, 2016)

Digging Up Nature's Mechanisms: Surprises by Enzymes With Novel Metallocofactors

Metals are essential for life, from viruses to the cells of the human body. Metals such as iron and magnesium are needed for proper cell function. Because of the indispensable role they play, it is important to understand how they function in cells. Dr. Pandelia discussed her recent work examining the role of metals in different cellular processes. For example, her work has determined that iron and sulfur are essential for the formation of lipoyl cofactor, which is needed for metabolism. She also discussed the hepatitis B virus, which contains an unknown metal that is responsible for the growth of cancer in the liver associated with the virus. Her work highlights the multiple roles metals can play in cell biology.

My presentation was segregated into two parts, regarding the role of complex metallocofactors involved in enzyme catalysis and function.

The first part of the talk was dedicated to the enzyme Lipoyl Synthase (LipA). LipA catalyzes the last step in the formation of the lipoyl cofactor, which is critical to aerobic metabolism in various 2-oxoacid dehydrogenase complexes. LipA employs two [4Fe-4S] clusters to successively insert two sulfur atoms at the unactivated C6 and C8 positions of a protein-bound octanoyl group. In this reaction, LipA uses one of its [4Fe-4S] clusters and AdoMet to produce the 5′-deoxyadenosyl radical, which abstracts a hydrogen atom from substrate before each sulfur insertion. The role of the second [4Fe-4S] cluster was unknown. We have employed kinetic and spectroscopic analysis to investigate the structure and mechanism of LipA. Our results showed that LipA adopts a "cannibalistic" mechanism, whereby it sacrifices the second [4Fe-4S] cluster to provide sulfur for the formation of the lipoyl cofactor substrate, thus limiting the enzyme to one turnover *in vitro*.

The second part of the talk was about a small viral protein, designated protein X, which is an oncogenic factor in chronic infections affected by the Hepatitis B virus (HBV). Protein X is the smallest gene product of HBV and the main etiological agent of virus-mediated liver oncogenesis. Although there are innumerable reported functions and protein binding partners, the molecular mechanisms by which protein X promotes tumorigenesis are still unclear. Despite the multi-decade studies, hardly any biochemical or structural information is known, which has been the major obstacle for linking its structure and activity to the cascade of cellular processes it modulates. We have shown that HBx harbors a novel, previously unrecognized metallocofactor, thus opening the avenues for its characterization. Our findings are consistent with the metallocofactor being not solely a structural element, but having an active redox and structural role in the biological activity of protein X.

Ben Rogers, PhD
Department of Physics
Brandeis University
(October 17, 2016)

Using DNA to Program Pathways in Complex Self-Assembly

What if a battery could stay charged for decades? What if medications could be delivered directly to diseased cells without harming healthy ones? Nanomaterials research is bringing these possibilities closer to reality. A nanomaterial has an internal structure similar to the same material on a larger scale, but has been genetically modified to exhibit different characteristics. Dr. Rogers discussed his work using modified DNA strands to design an altered self-assembly pathway for colloids (a non-crystallizing substance such as a gel). His work highlights how this altered DNA can lead to different behaviors and assembly phases as the colloid structure builds itself. This research could be useful for the nanotechnology goal of creating devices that can respond or change structure on demand.

DNA is not just the stuff of our genetic code; it is also a means to build complex materials. Grafting DNA onto colloidal nano- and microparticles can, in principle, 'program' them with information that tells them exactly how to self-assemble. Recent advances in our understanding of how this information is compiled into specific interparticle attractions have enabled the assembly of crystal phases not found in ordinary colloids, and could be extended to the assembly of prescribed, nonperiodic structures. However, structure is just one piece of a more complicated story; in actuality, self-assembly describes a phase transition between a disordered state and an ordered state, or a pathway on a phase diagram. In this talk, I presented experiments showing that the information stored in DNA sequences can be used to design the entire self-assembly pathway, and not just its endpoint. Using grafted DNA strands to induce specific attractions between particles, and free DNA strands that compete to bind with the grafted ones, I showed that it is possible to create colloids with exotic phase behavior, such as arbitrarily wide gas-solid coexistence, re-entrant melting, and even reversible transitions between different solid phases. Going forward, this work could prove especially useful in nanomaterials research, where a central goal is to manufacture functional devices that can respond or reconfigure on demand.

Tijana Ivanovic, PhD
Department of Biochemistry
Brandeis University
(October 17, 2016)

Influenza Membrane Fusion: Insights From Single Virions Into Potential Avenues for Viral Evolvability

Influenza has always been a major health issue, but one that the general population does not consider overly dangerous. However, a major epidemic of influenza occurs roughly every 30 years. In 1918, the epidemic killed around 50 million people worldwide. In more recent times, the bird flu has led to serious outbreaks. But how does the flu make the jump from birds to humans? It is not the stuff of horror movies, but of genetics. Dr. Ivanovic discussed her work with an advanced microscopic technique, which allows her to image how influenza mutates and enters cells. This type of imaging can help to determine how the virus evolves and how influenza adapts to different species.

Influenza virus is well known for its ability to cause recurrent pandemics and presents an imminent threat to humanity. Pandemics occur every 30 years, on average, when a new influenza subtype mutates to infect humans from its natural avian reservoir, adapts to airborne transmission among humans, and spreads globally. Influenza outbreaks differ in severity; the deadliest one known to history is the 1918 influenza pandemic that caused about 50,000,000 deaths.

The influenza cell-entry protein, hemagglutinin (HA) is a key determinant of influenza pandemic adaptation. (H in the subtype nomenclature is based on the antigenic properties of HA.) To adapt to human infections, influenza changes HA receptor-binding preference from avian to human receptors. To adapt to airborne transmission, it produces more stable HA. Systemic infection characteristic of highly pathogenic viruses has been linked to the extent of HA activation by proteases. However, effects of molecular changes in adapted functions are multifaceted and often antagonistic, so that adaptation involves a balance between the functions that is appropriate for a particular set of selective pressures. To obtain a complete picture of adaptive molecular events, my integrated functional analysis enables separate measurements of different cell-entry functions, as well as measurements of their combined functional output.

In my talk, I summarized my recent work, which uses an advanced microscopy technique to enable unprecedented level of detail in the underlying molecular events leading to productive cell entry by influenza. I used total internal reflection fluorescence (TIRF) microscopy to image (in real time) a series of cell entry steps for hundreds of influenza virions at the resolution of individual virions. For these experiments, I created a panel of carefully chosen point mutants deriving from the known crystal structures of HA and the observed differences in cell-entry properties between two highly similar influenza strains. I further developed stochastic computer simulations to aid the interpretation of the single-virion experiment data. Combined, these analyses and their extensions to comparisons between more distant influenza strains, have set the stage for the goal of defining the molecular constraints on HA evolvability during cross-species adaptation.

The Volen National Center for Complex Systems Poster Session

The Volen Retreat offers the opportunity for all Volen-affiliated faculty, postdoctoral fellows, and graduate and undergraduate students to present a poster detailing their research. This is an opportunity for other members of the community to engage with their fellow scientists and exchange ideas. The face-to-face format of a poster session allows for direct and detailed discussion of data and techniques. This year, 19 postdoctoral fellows and students presented posters, as listed below.

Presenter	Poster Title
Daniel Acker	Controlling seizures by molecular manipulation of inhibitory synapse formation
Ramin Ali Marandi Ghoddousi	Delineating the active circuit involved in taste-associated learning and memory
Katelyn Daman	Elucidating the mechanism by which the GTPase Rem2 negatively regulates dendritic complexity
Maitreya Das	Construction and analysis of CRISPR-mediated KO models for KCNV1 in Pyramidal Neurons
Steve DelSignore	The Lowe Syndrome phosphoinositide phosphatase dOCRL restricts innate immune activation by regulating endosomal traffic
Danielle DiTirro	A Tubby Tale: Sensory signaling and membrane composition in *C. elegans* cilia
Nadya Greenberg	Motor resonance predicts dominance and behavior
Jessica Haley	The effects of acute changes in pH on central pattern generating circuits

The Volen National Center for Complex Systems Poster Session (Cont.)

Presenter	Poster Title
Anna Hartmann	Weighting of antagonistic sensory pathways underlies behavioral response valence to olfactory cues
Munzareen Khan	The GCY-29 receptor guanylyl cyclase shapes AFD-mediated thermosensory signaling in *C. elegans*
Kang Liu	Gradation of synaptic strength by quantal addition of structural modules
Jacqueline McDermott	The role of Class 4 semaphorins and plexinB receptors in GABAergic synapse formation
Nathaniel Miska	Independent regulation of 'feedforward' vs. 'feedback' E-I ratio following visual deprivation in a canonical V1 microcircuit
Anna Moore	Rem2 regulates distinct homeostatic mechanisms in visual circuit plasticity
Sarah Richards	Loss of SRGAP2A broadens tuning in primary visual cortex of the mouse
Asuka Takeishi	Molecular and neuronal mechanisms of feeding state-dependent thermotaxis behavioral plasticity
Alejandro Torrado Pacheco	Bidirectional firing rate homeostasis in V1 of freely behaving rodents
Nick Trojanowski	CaMKIV, homeostatic plasticity, and firing rate set points
Rylie Walsh	Retromer regulates APP-exosomes at the *Drosophila* NMJ

The M.R. Bauer Foundation Summer Science Research Fellowships

Introduction

The M.R. Bauer Summer Science Research Fellowship Program began on May 30, 2017 and culminated with each of the Fellows presenting a poster at SciFest VII on Aug. 3, 2017. For the fourth consecutive summer, the M.R. Bauer Foundation's gift supported undergraduate research projects. In 2016, ten budding scientists got an opportunity to conduct research in laboratories at the Volen Center for Complex Systems, which enabled these very talented undergraduates to tackle important research questions. More importantly, the M.R. Bauer Summer Undergraduate Research Fellowships supported the growth of each recipient as a scientist. As you will read in each Fellow's personal statement, the opportunity to pursue research this summer was life changing. These students not only gained practical experience and skills, but also developed as students and scientists. According to undergraduate student Miriam Hood, "The M.R. Bauer Fellowship not only facilitated the progress of my research, but has given me the time to build a strong foundation for a future in scientific research." Fellow Jessie Moore echoed these sentiments. She said, "Participating in this program has strengthened my passion for research and further driven my goal of contributing to science." Undergraduate Sabrina McDonnell also values her experience. She stated, "The funding I received enabled me to delve deeper into my project and become more confident in my abilities as a researcher."

It is due entirely to the generosity of the M.R. Bauer Foundation that these young scientists were able to experience what truly comprises laboratory life and science during the summer of 2017.

Miriam Hood
Theobald Laboratory
Department of Biochemistry
Brandeis University

Active Site Dynamics of a Bifunctional Apicomplexan Malate and Lactate Dehydrogenase Ancestral Intermediate

Poster Abstract

A variety of human diseases, including malaria, are caused by unicellular eukaryotes of the phylum Apicomplexa, which have evolved a highly specific lactate dehydrogenase (LDH) from malate dehydrogenase (MDH), which may be a potential drug target. A putative promiscuous intermediate in the evolutionary path makes Apicomplexan LDHs and MDHs an excellent model for studying the role of such intermediates in the evolution of specificity.

A six-amino acid insertion conferred pyruvate activity in LDHs, by shifting the key catalytic residue from an arginine in MDHs to a tryptophan. There are two hypothesized conformations for the active site of the bifunctional ancestor intermediate, but only an LDH conformation is seen in X-ray crystallography.

Heteronuclear single quantum coherence nuclear magnetic resonance (HSQC NMR) spectroscopy was attempted to visualize the enzyme in the presence of each substrate, but was unsuccessful due to the size of the tetramer formed. Disruptive mutations were used to create a stable dimer, small enough to produce a well-resolved HSQC NMR spectrum. HSQC NMR spectra of the dimer with oxaloacetate and pyruvate are well resolved, but do not show significant peak shifts.

Personal Statement

This summer marks my third and final summer as an undergraduate researcher in the Theobald Lab. I can say, without a doubt, that my time in the lab has been one of the most transformative experiences of my time in college. As an incoming first-year student, I knew I wanted to participate in undergraduate research, but I had no idea of just how involved I would become and how much I would come to enjoy and appreciate engaging in active fields of scientific research. In the Theobald Lab, I have come to see evolution in an entirely new light, one that is far more complex and deeper than the initial theory introduced in high school biology. I have had the opportunity to apply the method and theories discussed in my biochemistry courses to biologically relevant enzymes, dig further into scientific papers, and have meaningful conversations with graduate students and professors about the value of basic scientific research. Summer research, in particular, has be incredibly important to my time in the lab, allowing me to focus fully on my project for several intense and productive weeks.

The M. R. Bauer Foundation Fellowship has allowed me to continue my research on a bifunctional Apicomplexan malate and lactate dehydrogenase ancestral intermediate for the combined Bachelor of Science and Master of Science degrees in biochemistry. Over the course of this summer I have been able to fully characterize the kinetics of this ancestral intermediate, determine melting point data for the intermediate and related ancestors, and begin using new techniques, such as x-ray crystallography and fluorescence spectroscopy. Conducting this research has also allowed me to attend and present a poster at the annual Society for Molecular Biology and Evolution meeting. Attending the event and presenting a poster provided me with an opportunity to expand my presentation skills. The meeting also allowed me to discover just how broad and far reaching the field of molecular evolution is, and engage with other scientists who use a wide variety of unique approaches to the field. My time in the lab supported by the M.R. Bauer Fellowship, has not only facilitated the progress of my research, but has given me the time to build a strong foundation for a future in scientific research.

Sabrina McDonnell
Hedstrom Laboratory
Department of Biology
Brandeis University

Exploring the Function of IMPDH's CBS Domain in *Escherichia Coli*

Poster Abstract

Inosine 5'-monophosphate dehydrogenase (IMPDH) converts inosine 5'-monophosphate (IMP) to xanthosine 5'-monophosphate (XMP), as a part of the de novo purine biosynthesis pathway. IMPDH is a tetramer, and each monomer has two domains: a catalytic domain and a cystathionine β-synthase (CBS) domain. The function of the CBS domain is currently unknown. However, the enzyme remains catalytically active when the CBS domain is replaced with a short peptide scar (ΔCBS). Mutations in the CBS domain of human IMPDH have been linked to hereditary diseases including, but not limited to *retinitis pigmentosa*. Understanding the function of the CBS domain in *E. coli* will shed light on IMPDH's moonlighting functions. Previous research in the Hedstrom Laboratory suggests that IMPDH interacts with both RNA Polymerase Beta (RNAPB) and Ribosome. *E. coli* strains expressing Strep-II tagged IMPDH and ΔCBS IMPDH were constructed, and affinity purification was used, to test for the presence of these interactions. A western blot containing fractions from a Strep-II tagged wild type lysate failed to confirm any interaction between IMPDH, RNAPB and Ribosome. During subsequent experiments, formaldehyde cross-linking was used to chemically crosslink protein-protein and protein-DNA/RNA interactions prior to purification. The formaldehyde cross-linking experiment revealed possible binding partners, but the protocol still needs to be optimized. Once cross-linking conditions are optimized, samples will be sent for mass spectrometry to identify the protein(s) interacting with IMPDH.

Personal Statement

In high school, I developed a passion for science, but my school's limited resources prevented me from getting involved in bench research. When I started at Brandeis and decided to study biochemistry, I knew I wanted to work in a lab and explore the multitude of research opportunities available on campus. I used my first year at Brandeis to become accustomed to the rigorous demands of college level science courses, and prior to my sophomore year, I reached out to Professor Liz Hedstrom. I was interested in the work in developing new antibiotics, so I was thrilled when she brought me in for an interview and gave me a position in her lab. Senior Daniel Kats '16 demonstrated lab techniques and taught me the fundamentals I needed to complete basic scientific research. By the end of the year, I had acquired the skills to conduct experiments independently. I then applied for and received the Division of Science Summer Undergraduate Research Fellowship. My first summer taught me about my abilities as a scientist and showed me how challenging and rewarding research can be. Scientific research rarely goes according to plan, but each failure provides insight into an aspect of the project that has not been understood.

After completing a year of research for course credit, I applied again for summer funding and was fortunate enough to become an M.R. Bauer Fellow. The support I received enabled me to delve deeper into my project and become more confident in my abilities as a researcher. This summer I accomplished a great deal and moved closer to answering my research questions. Having the opportunity to work in a lab over the past two years has taught me many valuable lessons, including patience and perseverance.

Lily He
Marder Laboratory
Department of Biology
Brandeis University

How Does a Crustacean Neuronal Circuit Respond to Changes in Extracellular [K+]? (Part II)

Poster Abstract

Over the lifetime of a crab, the pyloric neuronal circuit faithfully maintains rhythmic motor output, despite various environmental disturbances. In this study, we investigated short-term and long-term responses to superfusions of saline with elevated potassium ion concentrations (2x) across animals. In the initial set of experiments, we superfused modified saline for 10 minutes at a time, and, in some animals, saw the pyloric circuit lose rhythmic activity and recover activity comparable to baseline during the washout. We extended this to longer superfusions of other elevated concentrations (1.5x, 2.5x, 3x) and saw the pyloric circuit partially or fully recover activity similar to the baseline condition within the hour or hour-and-a-half-long manipulation. These responses are indicative of (a) homeostatic mechanism(s) that allows the circuit to re-achieve a particular activity level despite altered environmental conditions. We also have preliminary data on the responses of the PD and LP cells from intracellular recordings that show the changes in the resting membrane potential of the PD cell, as well as changes in calcium envelopes and spike height.

Personal Statement

Fortunately, I have been working in the Marder Lab for almost two years now, and I've learned how to critically think about experiments, data analysis and experiment preparation, among many more things. Over this period, I have come to cherish the time I spent over the summer doing research, as it is the only time of the year that I can fully dedicate to experiments and immerse myself in my work. As a result, I have made significant forward progress in my intellectual development and scientific techniques, and invested a large portion of time investigating questions that have important implications for work in related fields and in medicine. Being a Bauer Fellow allowed me the opportunity to continue my laboratory research this summer.

Unfortunately this summer, I ran into far more barriers than expected. I began trying out new and more difficult techniques, but soon ran into difficulties associated with the myriad of electrical equipment. One day, my electrodes would be working perfectly, and the next, that same electrode would be inaccurate in its measurements, due to some small mechanical shift. My experiments became extremely time-intensive and, compounded with the daily technical difficulties, I found myself working late into the evening, sometimes even needing to carry into the next day. However, in experiencing these challenges, I learned to think on my feet more often and improved my ability to troubleshoot problems. I was also able to notice small differences in my setup that had led to those challenging issues. In a sense, I have come to see experimental setup as an experiment in itself. I appreciate the unexpected benefits of troubleshooting, the development of creative problem-solving strategies and greater patience with myself.

Richard Haburcak
Xu Laboratory
Department of Chemistry
Brandeis University

Ligand-Receptor Binding Modulates Supramolecular Assemblies of Small Peptides

Poster Abstract

Proteins and small molecules exhibit dynamic and intricate binding behavior in biological and biomedical domains. However, while enzymatic transformations that modulate the binding of proteins are common, it is rare for small molecules. We explore how a ligand-receptor binding interaction between Vancomycin and D-Ala-D-Ala modulates the morphology of supramolecular assemblies formed by enzyme-instructed self-assembly (EISA) of small peptides. Without the binding interaction, a precursor molecule is enzymatically dephosphorylated (to give a hydrogelator) and further assembles into long nanofibers; binding interactions cause the formation of precipitates containing short nanofibers. Additionally, by itself, the hydrogelator assembles into nanosheets or nanofibers that do not bind Vancomycin. Addition of a surfactant breaks up the assemblies and restores binding. Further, an excess amount of Vancomycin can disrupt the assembled hydrogelator. The presence of Vancomycin hence biases the assembly pathway, demonstrating how binding modulates self-assembly kinetics. As the first example of such a phenomenon for small molecules, we provide a solution to evaluate the interaction between aggregates and target molecules, and insight into emergent behavior of supramolecular systems.

Personal Statement

Undergraduate research has been a huge part of my college experience. Working in the lab before my freshman year, I found not only a place where I was comfortable but also a place where my opinions were respected and I was challenged. Summer research is an important aspect of the undergraduate experience, as the semesters present endless classes, reading, and assignments that leave hardly any time, at least in my case, for research during the school year. However, research has always been a time to get away from assignments and focus on questions that may have an impact beyond a grade.

Participating in research has not only allowed me to expand my knowledge and work with leaders in the field but to gain personal relationships with other professors at the university. In addition, participating in research has allowed me to work on projects that later went on to be published, including a paper on which I was the first author. This unique experience as a Bauer Research Fellow has pushed me to grow both academically, as many topics covered in courses held potential to be useful in future research. Personally, I have sought out opportunities to teach and mentor other undergraduates. Overall, my undergraduate career would be incredibly different without research, and much less fulfilling.

Abigail Daniels
Garrity Laboratory
Department of Biology
Brandeis University

Neural Circuit Control of Acute Cold Tolerance

Poster Abstract

The ability to maintain homeostasis during thermal shifts is essential to all life. This is especially important for insects, due to their small size and inability to regulate their body temperature. A lot is known about long-term cold tolerance in insects, but little is known about the mechanisms underlying acute cold tolerance. We have identified a novel cold tolerance mechanism in *Drosophila*, in which the mushroom body mediates peptidergic signaling to regulate heart rate and rhythm during cold exposure. A direct physical and functional connection was shown between selected mushroom body output neurons (MBONs) and corazonin (CRZ) neurosecretory cells. This is a novel circuit that utilizes the mushroom body in non-traditional ways and reveals how MBONs are implicated in behavioral response.

Personal Statement

This summer, the M.R Bauer Fellowship gave me the opportunity to learn brain imaging techniques and *Drosophila* genetics. I became proficient with fly brain microdissections and multiple antibody staining protocols. In addition to the preparation steps for brain dissections, I have learned how to operate a scanning confocal microscope and have just started to take images independently. Additionally, with the guidance of my mentor, I learned the basics of *Drosophila* genetics and began a series of multi-step crosses to generate animals with complicated genetic backgrounds. This fellowship provided me with the time and opportunity to expand my practical knowledge of microscopy and genetics. Through these experiments, I can better understand how we can reliably manipulate these organisms and address a wide range of neurobiological problems. I grew as a scientist over the summer and have developed the skills to tackle more complex and interesting experiments

Abraham Cheloff
Miller Laboratory
Department of Biochemistry
Brandeis University

Characterization of Monobody Interactions with EC2 Fluoride Ion Channel by Fluorescence Anisotropy

Poster Abstract

The Fluc ion channel family is comprised of dimeric membrane proteins functioning to expel excess F- from the cytoplasm of microorganisms to resist inhibitory effects of this environmental xenobiotic anion. Recent structures of an *E. coli* Fluc homolog, EC2, bound to engineered “monobody” proteins selected from phage display libraries, reveal multiple side-chain contacts at the channel-monobody interface. Two such monobodies, S9 and S12, share a similar interface structure, but their nanomolar-range binding affinities differ by ~5 fold. We focus on the per-residue energetic contributions to the binding affinity of S12 to Fluc by introducing point mutations at polar contacts on either side of the interface, assessing the change in binding affinity using fluorescence anisotropy. We have found that many of the residues on the diversified loops of S9 and S12 contribute significantly to the binding energy. Future studies will continue to mutagenize the monobody-channel interface to derive information on how these different monobodies interact with Fluc channels, and focus on obtaining crystal structures of S12 and its mutants to understand the implications of structural changes in these experiments.

Personal Statement

I was able to continue my research through the summer in Chris Miller’s lab due to the fellowship supported by the Bauer Foundation. I was presented with the opportunity to delve into different areas of protein science without many of the distractions of the school year, such as classes and extracurriculars. By focusing on the direction of my project, along with the acquisition of new skills and techniques, my project has grown significantly in breadth, and will hopefully continue to do so during the coming year. The summer research experience built my self-confidence in research, gave me the resources necessary to overcome the steep scientific learning curve, and to complete more complex and involved procedures. The strides of accomplishment from this summer will allow me to continue with my senior thesis project in the coming academic year.

Jessie Moore
Griffith Laboratory
Department of Biology
Brandeis University

Exploring the Effects of Sleep by *let-7* on Mushroom Body Development in *Drosophila*

Poster Abstract

Drosophila rest is a sleep-like state and can be utilized to better understand the mechanisms of mammalian sleep. Both the mushroom body and circadian clock play a key role in *Drosophila* sleep regulation. *Let-7* has been found to regulate mushroom body development through its targets, such as *chinmo* and *abrupt*. *Let-7* is a microRNA, which are short, noncoding RNAs that help regulate gene expression. Inhibiting *let-7* produces a reduced sleep phenotype.

We aimed to further explore the involvement of *let-7* in mushroom body development and circadian rhythms, and the effects of two potential *let-7* targets, *abrupt* and *chinmo*, on sleep regulation. We found that *let-7* is not required in PDF+ neurons and that *chinmo* may also regulate sleep.

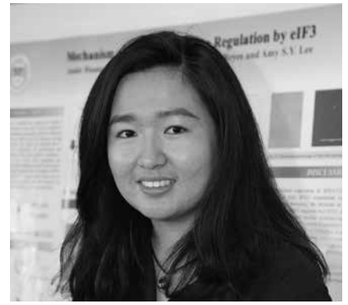
Personal Statement

This summer, I worked diligently to continue my research on the microRNA, *let-7*, and its role in sleep regulation in *Drosophila*. I have been working with this microRNA since sophomore year, but only during the academic year. I was fortunate to receive funding through the M.R. Bauer Foundation in order to focus on my research throughout the summer months. Without the stress of my academics, I was able to conduct numerous sleep experiments, perform DNA extractions, and even learn a new technique, brain dissections.

I am very grateful to the MR Bauer Foundation to have been given this opportunity. This summer has strengthened my passion for research and further driven my goal of contributing to science. My professional goal is to become a research physician, leading clinical trials and conducting groundbreaking research that will help the lives of many. My experiences this summer have encouraged me to pursue research in the future.

Annie Huang
Lee Laboratory
Department of Biology
Brandeis University

The Mechanism of BTG1 Translation Repression by eIF3



Poster Abstract

All cells in our bodies contain the same DNA, but we are clearly made up of many different types of cells. This is due to, and is the result of gene regulation. Gene regulation is essential for eukaryotes because it determines what a particular cell can do by controlling when to express a certain gene. Gene expression can be regulated at many different stages including transcription of DNA to mRNA, as well as the translation of mRNAs to proteins. Translation is mostly controlled at the level of initiation, which involves the interactions between mRNA, initiation factor, and ribosome. Previous studies by Dr. Lee have shown that eukaryotic initiation factor 3 (eIF3) is responsible for regulating cell proliferation and differentiation by its interactions with two mRNAs that encode c-JUN and BTG1. The eIF3 complex upregulates the translation of c-JUN by directly binding to the c-JUN stem-loop structure and downregulates the translation of BTG1 in a different, as yet unidentified, mode. However, it is known that the translation inhibition is stem-loop specific, as reversing the stem-loop does not result in the repression of translation. To understand how mRNA and eIF3 interact, we seek to identify the co-factor. We plan on taking two approaches. The first one is to use mass spectrometry to identify the co-factor, assuming it interacts with the stem-loop and eIF3 through direct binding. The second approach is to incorporate Green Fluorescent Protein (GFP) into the sequence and use the CRISPR/Cas9 system to target and knockdown certain proteins. Screening will then be performed to isolate and identify the co-factor. By understanding the mechanism of eIF3 in gene regulation, we hope to understand more about cell growth control and possibly the link to cancer.

Personal Statement

My time working in Amy Lee's research lab has been challenging, but rewarding. Dr. Lee is a new faculty member who established her laboratory in 2016-2017 and the lab was just a month old when I joined. The nascent lab has given me the chance to work closely with a small group of inspiring scientists and an enthusiastic mentor and the unique opportunity to learn more than just research. This experience has also demonstrated how one sets up and runs a lab.

Working full-time as a researcher, which is what I was able to do this summer as a Bauer Fellow, is a lot different from what I expected; it is more than just pipetting. Being a researcher is about problem solving, collaborating, thinking ahead, and the constant intake of new information. I am constantly challenged by unforeseen results. For instance, there was a day when I ran the same PCR four times and got completely different results each time. I never did figure out what went wrong, but sometimes that is science. Everything is about trial and error. Researching may not yield the most prolific results but this is what makes all the little discoveries so exciting and inspiring.

Kaitlyn York
Wingfield Laboratory
Department of Psychology
Brandeis University

The Use of Pupillometry to Examine Effort While Processing Noise Vocoded Complex Sentences

Poster Abstract

The pupil size of the human eye responds to differing light conditions and also increases in constant light with cognitive or attentional effort (Kahneman & Beatty, 1966). Noise vocoded speech has been used to simulate the experience of hearing speech transduced by a cochlear implant with different degrees of spectral resolution. This study examines the comprehension of sentences that vary syntactic complexity, plausibility, and number of spectral channels. While listening to these sentences that contain double or single negatives, young and older adults with normal hearing acuity are asked to recall the sentence. Pupil size is measured throughout, to determine if (despite similar levels of comprehension) pupil size shows relatively less dilation in response to sentences with higher spectral resolutions, indicating a reduction in effort needed to process those sentences. Successful results within this study would encourage an analogous study involving people with cochlear implants.

Personal Statement

I joined the Wingfield Memory and Cognition Lab as researchers in the lab are interested in looking at cognitive changes throughout aging. Once I settled into the lab and had a better understanding of the scientists' research, I was captivated by the prospect of looking at cognitive effort through online measures such as pupillometry. In the past, most of my time at the Wingfield Lab has been spent collaborating on a project looking at the benefits of speech prosody for older adults. As an M.R. Bauer Fellow this summer, my time was spent establishing my current project that will become my senior thesis. Throughout its development, I have learned how to normalize sentences, use a program to manipulate them to sound like speech through a cochlear implant and write a program to run the experiment. This opportunity has allowed me to learn about the large amount of preparation that goes into creating an experiment. It has also given me the chance to develop skills such as creating a computer program for neuropsychological experiments, along with collaborating with others and learning from their experiences. Furthermore, working in the Wingfield Lab has taught me the benefits of looking into every aspect of an experiment, especially potential confounding variables and analyzing every step along the way. Personally, the summer experience has shown me that I enjoy research and creating experiments, and that I want to this in the future. I thank the Bauer Foundation for making my summer of research possible.

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What Are Our Antibodies Binding to? Evolving an HIV Vaccine

Poster Abstract

Recent HIV vaccine research has focused on broadly neutralizing antibodies (bnAbs), which neutralize a wide breadth of HIV strains. One such bnAb, 2G12, binds to a conserved cluster of (GlcNAc)2-Man9 glycans on gp120, a trimeric glycopeptide on HIV's envelope. To elicit bnAb production *in vivo,* a library of glycopeptide mimics was synthesized via solid-phase peptide synthesis and a CuAAC reaction between L-Homopropargylglycines in the peptide and Man9-cyclohexyl-azide. The few mimics that were bound tightly by 2G12 were conjugated to a carrier protein and then used to immunize rabbits, hypothesizing that 2G12-like antibodies would result. Yet the polyclonal serum of the rabbits exhibited low binding to (GlcNAc)2-Man9. To determine what the elicited antibodies in the serum were binding to, the rabbit serum was tested against different fragments of the mimics. Indirect ELISA revealed that there is a strong antibody response against the core of the mimics: triazol-cyclohexyl-Man2, which is largely unnatural. Moving forward, refinement of this unnatural linkage to a less immunogenic form may increase the production of antibodies to Man9; antibodies that may bind better to (GlcNAc)2-Man9.

Personal Statement

As a rising sophomore, this summer was a headfirst dive into research. While I had started working in the Krauss Lab in January, the ball didn't start rolling until this summer, when I was awarded an M.R. Bauer Fellowship. With more time to learn the necessary immunology and chemistry, as well as read the key papers, the tediousness of pipetting came into a whole new light. In addition to building a context for my research, I developed a greater connection with both the material itself and the other members in our lab. Spending all my time in lab this summer truly helped me build an academic home in chemical biology and a personal home in the Edison-Lecks building.

As I look back on this opportunity, I see that another unexpected effect to this summer's work is how my research interests have shifted. When the summer began, I was more interested in the application of science; hence my joining Dr. Krauss's lab to work on vaccine design. Now I feel more inclined to do basic, curiosity-based, research. I find myself wondering less about how to get stuff to bind to sugars on HIV and more about why those sugars are there in the first place. In this regard, my interest in immunology has certainly been piqued. Because I'm also interested in physics and chemistry, this is opening some fascinating doors as to what I can do in the future.

Acknowledgments

As always, we thank the speakers who came to Brandeis this past year to share their research and to engage us in hours of stimulating discussions with Volen Center faculty, students and postdoctoral fellows. We are also grateful to our visitors for forwarding to us their lecture summaries that form the basis of this report.

We especially acknowledge Kim MacKenzie, a past neuroscience PhD graduate, for her valuable contributions and editorial assistance in the preparation of this report.

The text of this summary of the Bauer Foundation series, along with summaries from previous years, can be found at www.bio.brandeis.edu/bauer.

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